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Bronchogenic carcinoma

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BRONCHOGENIC CARCINOMA

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INTRODUCTION

In introducing this subject, it is well to first realize the most relevant fact, that the disease being considered has risen from a place of relative obscurity to one of major prominence in the last two decades. Therefore, one of the most important questions to be discussed in the following paper is whether this rise in prominence is apparent or real. To do so, it is necessary to have at hand much statistical evidence. This has been greatly simplified by the most commentable work of Dr. Edwin J. Simons, whose work on "Primary Carcinoma of the Lung", published in 1937, has lent great aid in compilation of all statistics and also as a guide for the following paper.

This paper has not been written as a review of the literature on the subject, but for the purpose of presenting to the reader a comprehensive review of the subject as it now stands. It is hoped that upon completing the paper, the reader, presumably relatively unacquainted with the subject, will have a better understanding and be more conscious of its import when confronted with an unusual lung condition, and consider it in his differential diagnosis.

HISTORY

According to Adler in 1912, the first case of pulmonary cancer was recorded by Agricola in his writings in the sixteenth century. From this time up to the beginning of the nineteenth century, quite a number of articles appeared. However, these did not recognize the condition as cancer but believed it was related to tuberculosis or a lymphosarcoma of the bronchial glands. All their writings were in reference to a disease of the respiratory tract, found in miners at the Schneeberg mines in Saxony.

The recognition of this disease as being carcinomatous in nature, according to Simons (1937), belongs to Morgagni who, in 1761, presented a case which in autopsy revealed an "ulcus cancrosum" of the lung. Following this, several men reported cases but these cannot be definitely classed as carcinomas.

Bayle, in 1810, described a case in which he found both tuberculosis and carcinoma. Barron (1922) stated that Bayle spoke of this as "phthisie cancereuse". From this time on cases began to enter the literature. Laennec, doing pioneer work on the pathology of lung tumors, described tham as "encephaloid", a term which remained in use until Virchow devised a better classification.

According to Simons (1937), Reinhardt collected 28 cases from the literature, Wolf, in 1895 found 31, and in 1896

Passler assembled 70 cases and added four of his own. In 1904, Sehrt, in reviewing the literature in reference to a case of his own found 177. It was in 1912 that Adler published his famous monograph on the subject, reporting and reviewing 374 cases.

INCIDENCE

In opening the discussion on this phase of primary carcinoma of the lung, it is worth noting the belief of a large number of practitioners that this is a rare condition and seldom enters their minds when a vague chest problem presents itself to them. To substantiate the above statement, Schall, in 1928 quoted from five leading testbooks of medicine, namely, Osler, Coplin, Tice's Medicine, Oxford Medicine and Nelson's Medicine. All of these textbooks stated that primary carcinoma of the lung is a rare disease. Arkin and Wagner, in 1936, after reviewing a representative number of cases, stated that primary carcinoma of the lung is one of the most frequent forms of malignancy in the adult and went further to show that it ranks second only to gastro-intestinal carcinomas and constitues six to eight percent of all tumors.

The question at hand, in relation to incidence, is whether the increase in primary long carcinoma in the last two decades is apparent or real. Klotz, in 1927, reviewed the literature showing that there has been an increase in the percentage of pulmonary carcinomas of all autopsies for some period. Rheinhardt, in 1878, showed that primary carcinoma of the lung was found in 0.057% of all autopsies: Fuchs, in 1885, 0.065%, Passler, in 1894, 0.083%, Wolf, in 1894, 0.223%, Oestrom in 1907, 031%, Briese, in 1916, 0.46% and Barron, in 1922, 0.9%.

Regarding the increase in the United States and Canada, Simons (1937) points out that the first indication was in a special report

of the Bureau of Census in 1914. This attributed 371 of 52,420 deaths from all forms of carcinoma to cancer of the lungs and pleurae or in other words 0.6 per 100,000 population.

Moise, in 1921, stated that primary carcinoma of the lung constituted 1 per cent of all carcinomas or 0.36 per cent of all necropsies. To confirm his work, Moise showed in Adler's work, in 1912, and that of Scott and Forman, in 1916, that his figures ran true. In his own work he showed five cases of primary pulmonary carcinoma out of 375 necropsies which had a total of 29 cancers of all types making it 1.38 per cent of all necropsies and 17% of all carcinomas.

Wells, in 1927, found a total of 403 carcinomas with the involvement of thirteen different organs, seventeen of them or 4.2% being in the lungs. He went further to show that although to the clinical observer, external carcinomas appear to be the most frequent, actually, as proven by necropsy, the reverse is true, and presents a table showing carcinoma of the lung, breast and liver to be of equal frequency, while that of the skin is the rarest.

Jaffe' in 1935 showed that carcinoma of the lung was third in 6,800 autopsies at Cook County Hospital or 11.47 per cent of 871 carcinomas. Jaffe' also found that regardless of whether primary carcinoma of the lung is increasing actually or not, it is common enough so that everyone should be thoroughly familiar with it.

In an editorial in the Journal of the American Medical Association, in 1937, it is stated that cancer of the lung is unmistakably increasing in frequency and this is not due solely to improved diagnostic technique and postmortem studies. It is

also stated that in the last two decades, it has come to occupy a place second in importance to malignant growths of the stomach, uterus and rectum.

In 1927, McCrea, Funk and Jackson stated that in the old statistics, primary carcinoma of the lung was considered 1% but that now, from Hamburg to Leipsig, it ranges from 9.4 to 15.5%. The conclusion reached is that although there is an increase in this country, it is not of near the degree seen in Europe.

Barron, 1922, in reviewing the statistics derived from the Department of Pathology of the University of Minnesota showed that in the period from 1899-1911 there were 1,333 autopsies with no record of primary carcinoma of the lung while in the period from 1919-1921 there were 1,003 autopsies with 0.9% carcinoma of the lungs. Simons (1937) shows that recent surveys at the same institution reveal the same relative increase.

Simons (1937) in an effort to prove the absolute increase in frequency of primary carcinoma of the lung in the United States and Canada compiled a table representing eleven authors and 22,754 autopsies with 532 pulmonary cancers. This table shows a gradual increase in the percentage of pulmonary carcinoma in total autopsies from 0.0 in 1899 to 1.55 in 1930 and a similar increase in the percentage of cancers of the lung in total cancers from 5.88 from 1910 - 1914 to 8.28 from 1925 - 1938.

As Simons (1937) pointed out, to review the Englis literature in an attempt to show the incidence in England is complicated by

the fact that most English authors do not segregate primary carcinoma of the lungs as one group but consider them as part of all intrathoracic neoplasms. Passey and Holmes, in 1935, made a study of the teaching hospitals of Great Britain. However, in studying the statistics from sixteen hospitals they found that eight showed no increase, three were indefinite and five showed a marked increase, and they were led to the conclusion that no evidence was found to support the general view that there was an increasing incidence in intrathoracic neoplasms.

Duquid, in 1927, reviewed the records from Manchester Royal Infirmary. He showed that up to 1886 there were 2,107 autopsies with a percentage of 0.24 intrathoracic tumors while in the period 1921-1925 there were 1,126 autopsies with a 2.57 percentage. The gradual increase in this period is remarkable because of its similarity to that found in the United States.

Simons (1937) in his review of the incidence in Germany gives one table which shows the increase in incidence of pulmonary cancers. This is significant because of its parallel to those in the United States and Canada, however, the total figures in Germany are higher.

Years	Author	Total Adult Necropsies	Total Cancers	% Lung Cancer in Adult Necropsies	Total Cancer
1895-1900	Feilchenfeld	3,831	507	0.57	4.3
1900-1905	Redlich	3,816	496	0.61	6.3
1908-1913	Bejach	5,604	692	0.58	4.8
1917-1922	Wahl	3,842	396	0.62	6.06
1922-1927	Wahl	3,372	438	1.69	13.00

In relation to incidence in other countries Simons (1937) has shown that there is a definite increase in pulmonary cancer. He studied statistics from the United States, Canada, Argentina, Great Britian, France, Germany, Switzerland, Czechoslavakia, Austria, Hungary, Denmark and Russia.

There are numerous factors involved as to why pulmonary carcinoma is increasing but none are definitely proven. In this relation Goltz, in 1930 attempted to answer the question, aside from the etiological viewpoint. He stated that one reason to be considered is that of increased human longevity with a resultant increase in the cancer age, thus implying that individuals formerly died, before reaching the age where they might have developed carcinoma. Another point which he suggested is the change in pathological classification, resulting in more recent years in terming the former mediastinal sarcomas as primary carcinoma of the lung. Also he mentioned a point in which there is almost universal agreement and that is that with improved diagnostic methods there has been a more meticulous search of the lung at autopsy. He went on to state that he does believe there is an actual increase, however, because the percentage of lung carcinoma has increased three to four times to total cancer but that this increase is not as great as statistics would indicate.

ETIOLOGY

In opening the discussion of etiology of primary carcinoma of the lung one must realize that if the increase in incidence of this condition is real, then there must be some answer to this question because the increase is out of proportion to the development of malignancy elsewhere. Simons, in 1937, discussed fourteen different etiologic factors to be considered here.

HEREDITY:

Heredity has been considered as a factor in development of malignancy of any type and for any one type, such as the primary pulmonary carcinoma, a conclusion can only be reached after a critical survey of a number of cases. In reviewing cases, there are many in which no mention is made of heredity thus further complicating the picture. Weller, in 1929, stated that he believed that heredity might play a definite part in the development of these malignancies not directly but indirectly by an inherent predisposition aggravated by the numerous factors involved in chronic lung irritation. He believed that these factors act by being able to incite proliferation of certain cells in the repair and regeneration of them with the subsequent metaplasia and development of carcinoma.

To substantiate Weller's belief of an inherent predispostion, one can point to Bonser, who, in 1928, reported 176 cases, two of which had concurrent malignancies elsewhere; one had a cancer of the lip and the other a myxosarcoma.

Wright-Smith, in 1927, presented a case of unusual interest in which there were three primary neoplasms accuring simultaneously. There was a stomach cancer originally and at autopsy there was found an associated cerebral melano-endothelioma and an early medullary carcinoma of the bronchus.

However, to oppose this, Simons, in 1937 reviewed 930 cases with the object of compiling the frequency of an hereditary strain. There was a positive hereditary history found in 68 cases. It is interesting to note that 17 of these cases showed associated primary tumors elsewhere.

Therefore, it is concluded that heredity does not appear to play an important etiological part but that in certain isolated instances there is a general predisposition to development of malignancy in general as evidenced by those cases in which there are two or more primary tumors occurring simultaneously in the same individual.

TRAUMA:

In discussing trauma as an etiological factor in the development of any neoplasm, one must first consider the frequency of trauma in our present day life and often wonder if it isn't coincidental rather than the actual causative factor. Simons (1937) quoted Lubarsh who has set up certain criteria to be fulfilled before trauma is considered responsible for the development of any neoplasm. First, the injury must be severe, localized and produced prolonged damage at the exact site of the development of the

neoplasm to be formed, and second, that it was reasonable to believe that the injury might cause a neoplasm of the histological type presented.

Wells and Cannon, in 1930, presented a case of a man fifty years old who developed a primary carcinoma of the left upper lobe at the exact site where the patient had broken his 3,4,5 ribs eleven months previously. At the time of the original injury, there was absolutely no evidence of carcinoma, either radiographically or clinically. Death occured one year after the onset of symptoms. The authors believed, after a very careful study and analysis, that this was an instance in which trauma was the true factor in the production of the carcinoma.

Simons (1937) reviewed 500 cases and concluded that 19 were actually due to trauma. Thus, it is probable that trauma is a factor in rare instances, but does not warrant great consideration in etiology.

Causes of Cancer Among Schneeberg Miners:

In studying this, it is evident that in these mines there is a tremendously high incidence of primary pulmonary cancer ranging up to 53 per cent of all deaths. Also it must be realized that somewhere in these mines lies a very potent aggravating agent.

In an editorial in the Journal of the American Medical Association in August of 1932, it is pointed out that in both the Schneeberg and Joachimstal mines there are large radium deposits and that the air contains radium emanations up to 50 Mache units. This certainly arouses the suspicion that here could lie the inciting agent. The Joachimstal mines lie on the Bohemian side of the Erz mountains only twenty miles from Schneeberg.

Simons (1937) after reviewing the German literate on the subject says that the dust, containing its cobalt, arsenic, radium and fungi alone and in varying cominations, causes one to assume by necessity that they are the cause. He shows, however, that the variety of the agents said to be causative but with lack of definite evidence for any one alone or any combination still leaves the question unsolved.

PULMONARY TUBERCULOSIS

It was Bayle, in 1810, who first presented a case of pulmonary tuberculosis and pulmonary carcinoma. It was in 1925 that Cherry showed that cancer occurs more frequently in later life, those who have had an active tuberculosis earlier. He, therefore, propounded that this acquired resistance to tuberculosis was a predisposing factor to the developement of carcinoma. He felt that the cell of the bronchi and lung reacted differently to the same stimulus, that is, the tubercle bacillus.

Ewing was one of the first to consider tuberculosis as the cause of primary carcinoma of the lung. The fact that active tuberculosis and cancer can appear in the same individual is shown by Simons (1937) in his analysis of 2,941 cases in which he found 283 cases with a coexistint pulmonary tuberculosis or a ratio of 1:10. This, however, does not prove that pulmonary tuberculosis is necessarily a cause of pulmonary cancer.

Kramer and Som, in 1936, reviewed 300 cases of carcinoma of the lung with 100 post mortems. Out of these 100 cases, they found the cancer associated with a tuberculous cavity in only four cases and only two of these showed the cancer to be connected to the wall of the cavity. Fried, in 1931, stated that carcinoma

many times develops independently of the tuberculous lesion and in others it was found at the site of an old fibrotic infection.

Arkin and Wagner, in 1936, discussed seventy-four cases of bronchogenic carcinoma and found a tuberculous process in only three and decisively stated that pulmonary tuberculosis was not the cause.

Vinson, in 1929, stated a fact to disprove the belief that tuberculosis is a causative agent. He showed that the increase in pulmonary carcinoma has come at a time when pulmonary tuberculosis is on a decline.

In concluding this phase, one must admit that pulmonary tuberculosis is not a significant etiological factor but that in a few cases it must be definitely considered as casual agent, not as tuberculosis itself, but rather on the basis of chronic irritation.

INFLUENZA:

In discussing influenza as an etiological agent, one must be very open minded because it was coincidental with the flu epidemic of 1918 that there was noted the remarkable increase in incidence of pulmonary carcinoma.

It was Moise, in 1921, who reviewed the work on the influenza epidemic and showed the lungs to have very severe damage. This damage occurred to the

bronchial and alveolar epithelium with often striking and atypical epithelial proliferative changes resembling early carcinoma. Barron, who did his work in 1922, also is a strong proponent of influenza as an etiologic agent.

However, there are many adversaries of this theory and their works are just as convincing. One striking point here is that many of these adversaries are European men. Simons (1937) reviewed 795 cases and found only 55 with a positive influenza history; in other words only 7 per cent.

Again the point is reached in which nothing definite has been decided and that possibly in a few cases, influenza has been the inciting factor for the development of pulmonary carcinoma. However, influenza should be considered significant because it does comprise seven per cent of a sufficient enough number of cases as a positive history and may therefore act indirectly as an irritating agent with the consequent metaplasia.

PNEUMONCONIOSIS AND OTHER CHRONIC LUNG DISEASES:

Previousely, two specific lung diseases have been considered, namely, tuberculosis and influenza. Now the subject to be discussed includes numerous conditions, all of which are chronic inflammatory diseases

of the lung thus acting as chronic irritants and possibly materially contributing to the knowledge of etiology.

Moise, in 1921, along with his discussion of influenza gave considerable attention to these points. He sited cases which gave histories of chronic bronchitis or bronchopneumonia and went on to show that marked epithelial changes occur in these conditions and may be very suggestive. He pointed out that the difference between a typical epithelial proliferation in influenza as compared to the orderly repair following lobar pneumonia is very similar to the work of Winternitz, Wason and McNamara in 1920. They used intrabronchial insufflations of hydrochloric acid on rabbits and showed that weak solutions destroyed only the lining epithelium with consequent orderly repair. However, if the solution destroyed epithelium, basement membrane and a portion of the surrounding tissue, repair proceeded differently. Therefore it may be seen that repair occurs in an orderly fashion if the basement membrane is left intact. If the injury is more severe, the epithelium loses its orderliness and proceeds into the necrotic areas with a resultant picture of a malignant epithelial tumor. Therefore, one can realize the possibility of neoplastic growth resulting from a chronic inflammatory condition of the lung when that condition has proceeded

to the point where it destroys the basement membrance. This would appear to be the analogue of results obtained by Winternitz, Wason and McNamara.

Tuttle and Womack, in 1934, published their work which showed that repair of the bronchial epithelim occurs from the basal cells. These cells are at first low cuboidal but later become columnar. Therefore they reasoned that when the adult epithelium is subjected to a chronic inflammation, hyperplasia may occur. This hyperplasia may take the form of a metaplasia with the epithelium becoming stratified squamous. The fact that such a thing does occur and may be the first step in the formation of a carcinoma is very logical. However, Simons (1937) stated, statistical evidence is lacking in proof that such a thing develops in bronchietatic cavities and this is where Tuttle and Womack made their observations.

Simpson, in 1929, reviewed 139 cases and found that 40 of them gave a history lung trouble. Eighteen had chronic bronchitis; pleurisy, 11; pneumonia, six; influenza, five. Fried, in 1931, felt very definitely that when pulmonary cancer is found, it might well be traced back to a chronic inflammatory condition.

One specific disease should be mentioned because of its frequency, that is syphilis. There are varying

figures as to its presence in cases of pulmonary carcinoma and one fact should be kept in mind, that is the rarity with which it attacks the lung. Clerf and Crawford, in 1933, observed it but only once in 50 cases while Jaffe', in 1935, found it was present in 20 out of a hundred cases.

In concluding, it may be said that there is some relationship between the development of pulmonary carcinoma and chronic inflammotory disease of the lung. In review, it may be seen that there is no one disease responsible but it is the whole group. Also in the final analysis, it may be said that the end result is not due to the specific disease but is that conclusion which as been reached before, that is chronic irritation.

ROETGEN RAYS:

With the discovery of the x-ray, in 1895, and its ever increasing use, one must consider it as a possibility in the etiology of pulmonary carcinoma, although it as yet has no basis for consideration. It is a well known fact that x-ray burns and over-exposure has produced cutaneous carcinomas.

DUST INHALATION:

In considering this phase of the etiology, one can readily see its logic. Hampehn, as quited by Simons

(1937), actually considered pulmonary carcinoma as a dust inhalation disease and explained the increasing incidence of pulmonary carcinoma as due to the increased dust production as produced by our growth of traffic and industry. To be considered, is not only the dust content of the air, but also smoke and chemical impurities which is due to our increased industry.

Duquid, in 1927, pointed out the fact that since neoplasms of the lung arise from tissue directly exposed to atmospheric air, it would be logical to assume that this must be a specific pollution rather than general because with the smoke abatement act in England, the air was cleared of smoke but there was no decrease in pulmonary neoplasm as it would have been if the pollution had been general.

Kennaway and Kennaway, in 1936, analyzed 18,280 death certificates of men who died between 1920 and 1933 as a result of carcinoma of the lung or larynx and showed that the group exposed to excessive and prolonged road dust had a high incidence of this form of carcinoma.

Berblinger and Kikuth, as quoted by Simons (1937) both believe that dust has little place in the etiology of pulmonary cancer. They did this by showing that small localities in Central Europe have showed an ap-

preciable increase in pulmonary carcinoma with little increase in traffic.

Therefore, in concluding, it may be seen that dust may play a part in the production of pulmonary neoplasms in certain instances but as sole agent, it is not. It no doubt acts, when present, as a chronic irritating agent.

INHALATION OF TAR PARTICLES:

To attempt to establish the role of tar in pulmonary carcinoma, Murphy and Sturm, in 1925, worked on the external application of tar to a number of separated areas on the surface of white mice. They did this in such a manner that no single area was irritated long enough to produce skin lesions. This resulted in a high incidence of lung tumors, the incidence being 60 per cent in one series and 78.3 per cent in another. The control series developed no carcinoma. The tumors produced were exactly similar to spontaneous lung tumors in mice. These workers did not believe that the tumors were transmitted from the skin, nor did they believe that the tar was licked from the skin, swallowed and reabsored in the intestine, thence to the lung. Their conclusion was that the tar lowered the animal's resistance to carcinogenesis with the inhalation of irritating substances and

subsequent cardinoma.

Simons, (1937) quotes Kimura in that he was able to produce pulmonary cancer in one rabbit and three guinea pigs by insufflation of tar through a tracheotomy tube. Also, Von Meyenburg reported a case of pulmonary cancer in a hair-dresser, engaged in the manufacture of tar soaps. This should direct attention to the possible relationship between the increase in pulmonary carcinoma and increased tarring of reads.

Among the foreign literature, as reviewed by Simons, there are many debates as to the belief that tar particle inhalation is related to lung carcinoma. However, it seems to be the majority that feel that it is related and again it may be added to the long list of chronic irritants.

MOTOR-EXHAUST FUMES:

Duquid, in 1927, mentioned the fact that motor exhaust fumes could have a role in the production of lung cancers. Klotz, in 1927, pointed out the parallelism between the increase in pulmonary carcinoma and increased use of automobiles.

In this line, Passey and Holmes, in 1936, stated that there are two schools of thought about the automobiles. One is that the motor exhaust fumes is to blame while the other holds that it is the tarred roads.

They go on to show, however, that neither garage workers nor professional drivers are prone to lung cancers.

Simons quotes Schmidtmann, who reported in 1926, that waste gases from gasoline motors have no effect on the bronchial epithelium even after prolonged exposure. This differs from oil-driven motor wastes in that they cause marked destruction to lung tissue. However, no malignant formtion has as yet been observed.

There may be some relation of motor exhaust fumes, but it appears as yet too indefinite to consider.

WAR GASES:

Klotz, in 1927, and Brockbank, in 1932, mentioned war gases as a possible etiological agent. Numerous foreign articles have appeared giving this phase consideration. Klotz and Brockbank mentioned this because the former had three cases with a previous history and Brockbank, four.

Hoffman, in 1929, however, showed that the total hospital admissions for gas poisoning in the American forces were 70,552 with a total of 1,221 deaths. Not a one of these deaths was due to carcinoma of the lung. He also reached the same conclusions, that war gas is not a factor, after reviewing 3,014 gas fatalities.

Nolan, in 1932, made a stastical study of 1,250

autopsies in Veterans Administration Hospitals and found eleven pulmonary cancers among 120 of all types. However, none of these eleven cases gave a history of exposure to war gases.

Therefore, it must be concluded that war gases have a very small, if any, part in the etiology of lung cancers.

INDUSTRIAL AND OCCUPATIONAL HAZARDS:

In Duquid's occupational analysis, in 1927, he considered all intrathoracic tumors thus confusing the picture somewhat. He found that the largest number in any one occupation was twenty-eight, classified as laborers. Next came nine carters and then eight clerks. His final conclusion showed that the majority were in laborers but this did not mean that indoor workers were exempt by any means because several public men died of the condition.

Brockbank, in 1932, compiled 898 cases from the literature to show the relationship between occupation and carcinoma of the lung. This revealed that 19 per cent were laborers, 15 per cent unspecified but dusty occupations, and 13 per cent were houseworkers. The remainder were among the other numerous occupations but all of low percentage.

Andrus, in 1935, reported 64 cases, none of which he believes showed an occupational or industrial hazard

as an etiologic factor. However, Rosedale and McKay, in 1936, stated that they believed pulmonary carcinoma was more predominate in persons working under irritating atmospheric conditions.

In conclusion, it appears that possibly one can lean toward the side that believes occupational and industrial hazards do play a part but only a minor one.

Again it must be stated that if this is true, its' role is that of chronic irritation.

TOBACCO SMOKE:

Adler, in 1912, noticed the predominance of males over females in his 374 cases and attributed the difference to irritation caused by smoking. In one of the four cases reported by Scott and Forman, in 1916, there was a definite history of exposure to smoke and chemical vapors.

Hoffman in none of his 36 cases, reported in 1928, did he find evidence of nicotine absorption believing that nicotine was the irritating agent. However, in the history of 29 cases, smoking had been indulged in.

Among Arkin and Wagner's 135 cases in 1936, ninety per cent were chronic smokers and they concluded that it was an important factor in producing bronchial irritation. However, Passey and Holmes, in 1935, made the timely observation that if increased smoking was an important

factor in the increase in pulmonary carcinoma, then carcinoma of the tongue, pharynx and larynx would have likewise increased.

Therefore, smoking over a long period may be a lung irritant and may be considered a cause of pulmonary carcinoma but it cannot be said to be important with the information at hand at the present time.

GENERAL HYGIENE:

The German writers, according to Simons, have shown that by improvement of general hygiene and sanitation of the Schneeberg region, the incidence of pulmonary carcinoma has decreased.

Here, as in any disease process, the matter of hygiene is one of the first principals put to use when an attempt is made to eradicate or more efficiently control a disease.

CONCLUSIONS:

No further conclusions need be stated because the importance of each phase of etiology has been given immediately upon finishing it. One point might again be emphasized and that is that the etiology, regardless of what is discussed, has been summed up in one phase, CHRONIC IRRITATION, whether that irritation be mechanical, bacterial or radioactive.

PATHOLOGY

Ideas on pulmonary carcinoma have changed considerably throughout the history of the disease. As has been pointed out previously, one of the reasons contributing to the increase in incidence of lung cancers is that up to 1926 many of the lung tumors were thought to be mediastinal sarcomas, the so-called "oat cell sarcoma". These "oat cell" tumors are almost universally accepted, at the present time, as being bronchogenic carcinomas of the undifferentiated type. Throughout this earlier period, a gross classification was not made because the true origin of the tumor was not realized.

Although microscopic classification has been attempted since the time of Laennec, it has not been until the last decade that a satisfactory one has been reached and that is because it was only until recently that the true pathology of the condition has come to the front. Another tumor has been considered as primary, the superior pulmonary sulcus tumor. This was first reported in 1932 but there is still quite a heated debate as to its exact nature and whether or not it should be included in the classification of pulmonary carcinomas.

MACROSCOPIC FEATURES:

As to site of origin of these tumors, Weller, in

1913, reviewed 90 cases and showed that 90 per cent of these were bronchial in origin and originated at the hilus. There have been certain authorities who contended that the tumors arose in a specific part of the bronchial tree; that is, large bronchi or bronchi of the first or second order. Kramer and Som reviewed 100 cases in 1936 and showed, rather, that the large bronchus is the commonest site of origin. Their figures show that 62 per cent arise in the large bronchus, 18 per cent in the small branch bronchi with the remained arising from the parenchyma.

In considering the size of the tumor it should be kept in mind, as Carman in 1921 pointed out, that the size of the tumor may be infinitely small but with sufficient metastases to cause death. There may be extreme variations in size and in reviewing the literature on this point they may be said to vary roughly from the size of a man's thumb to the size of his head.

As to gross appearances of these tumors, Tuttle and Womack, in 1934, state that early there is a piling up of the mucous membrance which gradually extends along the mucosa and then protrudes into the lumen. As the neoplasm extends out into the lung parenchyma, it does so by finger like projections in a centrifugal direction. As this extends there may be various stages of

necrosis and abscess formation in it. They describe another picture which is not as common. This is one of diffuse growth resembling, somewhat, the gray hepatization of pneumonia. Olson, in 1935, reported 69 cases at which time he attempted to correlate the gross appearance with the microscopic picture. He stated that the adenocarcinomas were gray and firm with scattered areas of visible mucus. The undifferentiated group were found to be softer and pinkish in appearance. These tumors were prone to be hemorrhagic and show cavitation. As to the squamous cell tumors, he found that three-fourths of them were single, hard, gray masses while the other fourth were multiple hard tumor nodules.

For a classification of the gross lesion, Moise, in 1921, described three forms. The first form is the infiltrative type and the most common; next is the rather rare nodular type and third is the miliary form resembling the miliary tuberculosis. Kramer and Som, in 1936, divided their cases into three gross groups: (1) carcinoma of the large bronchus which comprised 62 per cent of their cases; (2) carcinoma of the small branch bronchi comprising 18 per cent; (3) carcinoma of the parenchyma, the remaining 20 per cent. These classifications can be very wide and varied but should not attract too much attention because the recognition of the

disease is not accomplished by study of the gross picture.

A tumor arising in the large bronchus or one of the branch bronchi can and does act as a foreign body as it grows and occludes the lumen. From this action, one can anticipate the resulting picture before death intervenes. As an example of this, one can cite the 24 cases reported by Klotz in 1927. Nine of his cases howed atelectasis, eight improper drainage and abscess formation and seven complete destruction of the bronchial lumen. Partial or complete bronchial obstruction in 18 cases showed a broncho-pneumonia, the direct cause of death at that time in the course of the disease. As another example of the complications, Arkin and Wanger, in 1936, showed that 47 per cent of their 74 cases had pleural effusion, 43 per cent bronchi-ectasis, 28 per cent acute pneumonia, 20 per cent chronic pneumonia, 20 per cent abscess or gangrene and 10 per cent a purulent bronchitis.

MICROSCOPIC FEATURES:

In beginning a discussion on microscopic features, it would seem proper to first consider the oat cell tumors which, up to 1926, were considered sarcoma and not bronchial carcinomas. As Simons (1937) points out, with the acceptance of these tumors as carcinomas, the per-

centage of bronchial carcinomas goes even higher. He compiled, from the English literature, a total of 472 cases of intrathoracic neoplasms. Of these, 38 per cent were classified as oat cell growths while only 29 per cent were obvious carcinomas.

Barnard, in 1926, rather conclusively proved that the oat cell tumor was a carcinoma. His conclusions were based on a macroscopic and microscopic study of character and method of dissemination of 19 cases of malignant tumors of the lung and mediastinum. Seven of these were obvious carcinomata and the remaining would have been classified as "oat-celled sarcomas." He found that when sections of obvious carcinoma were examined, small oval cells identical with those of the "oat-celled sarcomas" could always be seen in addition to the squamous, large polygonal or cubical cells which predominated. He also showed that in the "oat-celled sarcomas", he could demonstrate squamous, large polygonal or cubical cells as well.

To further substantiate this work, Boyd in 1930, stated that no tumor was perhaps as pleomorphic in character as that in the lung. His microscopic classification was: (1) anaplastic, (2) medullary, (3) adenocarcinomatous, (4) squamous. He went further to show that different forms could predominate in different areas of the tumor. He stated that by silver staining

one could demonstrate the essential carcinomatous character of even the most anaplastic form.

The superior pulmonary sulcus tumor was discussed by Pancoast in 1932 with report of seven cases. He believed that he had found a new entity. In only two was the microscopic picture studied and these both showed obvious carcinoma. Pancoast did not believe that this was a pulmonary tumor but arose from embryonal rests, possibly from the fifth pharyngeal pouch. Many men have worked on this and according to Simons (1937) this is not a distinct entity but may arise from bronchioles in that region and have the same clinical picture derived from any tumor at the thoracic inlet; that is, pain around the shoulder and down the arm, Horner's syndrome, and atrophy of the small muscles of the hand.

With regard to a microscopic classification, numerous ones have been devised. They are very elaborate but when the pleomorphism is considered one must try to get something more simple to fit the complicated picture. As an example of the modern classification and the frequency of the cell types, that of Arkin and Wagner in 1936 is most classical. In 74 necropsies, they found 28 per cent were adenocarcinomas, 24 per cent were squamous cell carcinomas and 41 per cent were of the undifferentiated group.

HISTOGENESIS OF PULMONARY CARCINOMA:

It was Adler, in 1912, who first advanced the theory that all primary pulmonary carcinomas arise from the bronchial epithelium and not from the alveolar epithelium. However, Barron, in 1922, stated that most of these malignancies arise from bronchial epithelium but that some arise from the bronchial mucous glands and alveolar epithelium.

Fried, in 1929, stated definitely that pulmonary carcinoma is bronchogenic. He went further to show that the lining of the alveoli is mesenchymal in origin and therefore could not develop carcinoma. He goes on to show that this carcinoma can not be derived from the bronchial mucous glands either. In 1931, the same author stated that there are three varieties of cells lining the bronchi, namely ciliated columnar, goblet and basal cells. The latter are the only ones concerned in regeneration and thus in formation of a carcinoma. He stated that primary squamous cell and basal cell epitheliomas do not result from metaplasia of preexisting ciliated columnar epithelium but originate from protoplasia (indirect metaplasia) of undifferentiated basal cells of the bronchial mucous membrane..

Weller, in 1929 b, studied 14 cases histologically with this in mind. He stated that there was no more than

presumptive evidence that any of these tumors arose from alveolar epithelium.

Tuttle and Womack, and Rabin and Neuhof, in 1934, both considered that all primary lung carcinomas were originated in the bronchial epithelium. Arkin and Wagner, in 1936, stated that all these tumors are bronchial in origin.

Therefore, it may be said that the concensus of opinion shows that all these tumors arise from the basal cells of the bronchial mucous membrance. Therefore, the term, bronchogenic carcinoma, may be given with absolute exactness to all primary carcinomas of the lung.

LOCATION OF TUMORS:

McCrae, Funk and Jackson, in 1927, showed in their cases that 40 per cent were on the right side and 47 per cent on the left side. Nine per cent were on both sides at or near the bifurcation. Four per cent were undetermined.

Olson, in 1935, stated after reviewing his 69 cases that the left and upper lobes were the most frequent sites. However, Arkin and Wagner, in 1936, found the right upper lobe to be the most frequent site.

Simons (1937), in order to determine the correct answer to this question, reviewed 2,177 cases and found that the right lung was involved in 1,147 cases, and

left in 992 cases and both in 38 cases. He also reviewed the literature to determine lobe frequency and found upper left lobe showing very slightly, a higher frequency than the right.

METASTASIS:

In considering this phase, one should realize that the lung acts as an anatomic barrier to embolic malignant cells which reach it via the blood stream from other organs. When, however, malignant cells arise in the lung tissue proper, many more malignant cells pass through the left heart and into the peripheral circulation. This is probably the answer to the rather peculiar mode of blood stream metastases and their secondary sites.

Metatases of this carcinoma, as in any carcinoma, occur via the blood stream, lymph stream or by direct extension. All or any combination of these may occur. Simons (1937) quotes Karrenstein as showing that in his 27 cases, 29.6 per cent metastasized through the blood stream and 18.5 per cent through the lymph stream as nearly as could be determined.

This carcinoma probably shows metastases to the brain more commonly than any other. McCrae, Funk and Jackson, in 1927, remarked about the frequency of sec-

ondary deposits in the brain. Davison and Horwitz, in 1930, selected 12 cases from 109 to be studied from the viewpoint of metastases to the central nervous system and the remarkable part of their work lies in the fact that three cases showed spinal cord symptoms, due to compression following invasion and destruction of vertebrae by metastases. They remarked, however, in conclusion, that the spinal cord is rarely the seat of metastases from carcinoma of the lung. Arkin and Wagner, in 1936, after reviewing 74 cases coming to autopsy, showed that the brain was involved in 24 per cent of these cases.

Another unusual point in metastases of this carcinoma is that they show a high incidence of bone metastases. In fact, Rogers, in 1932, stated that carcinoma of the lung should be classified with the mammae, thyroid, prostate and suprarenals as showing an early tendency to metastasize, to bone. Scott and Leist, in 1917, noticed the frequency of metastases to bone, reporting 14 per cent in their cases. Arkin, in 1930, pointed out that in every case of bronchogenic carcinoma, a myeloid blood picture, hyperplastic periostitis or actual bone metastases should be sought for. Hirsch and Ryerson, in 1928, after remarking about the high incidence of bone metastases stated that these metastases may dominate the picture. They mentioned four patients, two of

which had bone tumors removed surgically during life which were called "primary endothelioma of bone which at autopsy were found to be metastatic from bronchogenic carcinoma". Arkin and Wagner, in their 74 cases in 1936, showed bone metastases in 28 per cent.

Eloesser, in 1925, remarked that metastases to the heart occur more frequently in bronchogenic carcinoma than in any other. Brunn, in 1926, reviewed 626 cases and found the heart involved in 21 per cent of these cases.

Barnard and Elliot, in 1930, reported two cases of unusual interest because of their metastases. These two cases gave the obvious picture of intestinal tumor causing obstruction. These tumors were, definitely in one and probably in the other, secondary deposits from primary carcinoma of the lung.

All of the above have been in relation to blood stream metastases. Now attention will be given to lymph stream metastases. A case illustrating the centrifugal manner of spread by the lymphatics was reported by Baden Evans in 1927. The lymphatics were involved in this order: (a) to the back along lymphatics accompanying dorsal branches of the intercostal vessels; (b) forward to the mediastinal glands; (c) upward along the thoracic duct and tributaries of the right lymphatic duct, to the

supraclavicular glands and thence to the axillary glands; (d) downward along the thoracic duct to the coeliac glands and those of metastases. His results show that the regional lymph-nodes are first in frequency; being followed by liver and then lungs. In relation to the lungs, other than by direct extension and blood or lymphatic transportation, Atkin, in 1931, mentioned the possibility of secondary deposits in the opposite lung due to aspiration of malignant cells via the bronchus. Following the lung in incidence and in decreasing frequency are bones, kidneys, adrenals, cervical nodes, heart, thyroid, spleen, etc.

Fried made the observation that, as is the rule in all malignancies, soft, cellular tumors metastasize much more readily than the firm, scirrhous type. This places the undifferentiated type first, followed by the adenocarcinoma and lastly, the squamous cell type in order of frequency of metastases.

As to frequency and period of metastases, Tuttle and Womack found that a large tumor will remain localized in the lung for a long time but again death may occur early from etastases. Rabin and Neuhof, however, contend that parenchymal and peripheral types are characterized by late metastases, and these cases do not die from the pulmonary carcinoma, but years later from

distant metastases. The concensus of opinion seems to be that metastases occur in 50 per cent of cases, while some state that regional lymph nodes are almost always involved.

THE CLINICAL FEATURES

The part dealing with incidence etiology and pathology has received great attention and space in the literature. This is of great academic importance, however, even of greater importance is the clinical side of the problem. This is of great importance because it is by the very early recognition of bronchogenic carcinoma, as in all carcinomas, that progress may be made in the treatment and cure of the disease.

SEX INCIDENCE:

It has long been noted by writers on this subject, that this condition is found predominantly in males. The ratio, as compiled by various authors, varies considerably. In 1924, de la Camp reported fifteen cases, all of which were men. Atkin, in 1931, reported 93 cases seen at autopsy and his ratio was 80 men to 13 women. Arkin and Wagner in their review of 1135 cases found men to have a 12 to 1 higher incidence than women.

Simons, in 1937, computed the ratio from 4,101 cases in an attempt to more correctly formulate a ratio of sex incidence and found the ratio to be four males to one female.

AGE INCIDENCE:

There are not so many inconsistencies in age inci-

dence and it is generally agreed that the minimum age is 35 years in 75 per cent of the cases. Brunn, in 1926, showed that 90 per cent of the 576 cases he reviewed occured between the ages of 40 and 80. Beardsly, in 1933, reported a case of a 10 months old baby in which the first metastatic lesion was treated at that time.

Simons, in 1937, again tried to arrive at accurate figures by compiling 2,796 cases. This showed that more than one-third of the entire group occurred between 50-59 years while 80 per cent occurred between the ages of 50-70.

GENERAL CLINICAL FEATURES:

Chandler, in 1935, showed 16 cases representing 16 different manifestations of bronchogenic carcinoma and how they can vary. He began by showing the small nodule in the bronchi and how it may be almost completely asymptomatic. He went on to show how a neoplasm may have a ball valve action with the production of an emphysema. He showed the atelectatic picture with the drawing of the mediastinal structures toward the collapsed lung. He showed bronchiectasis with suppuration and another with an initial pneumonia distal to the new growth. He then went on and showed larger tumors with a pleural ef-

fusion or being so large as to push the mediastinum to the opposite side.

CLINICAL CLASSIFICATION:

It has been shown that a clinical classification is of great importance in view of treatment and prognosis. Tuttle and Womack, in 1934, made the simple classification as to whether the tumors arose in the major bronchi or in a minor bronchus. Rabin and Neuhof also in 1934 classified their tumors as being circumscribed or non-circumscribed. Their non-circumscribed group comprised three-fourths of their cases and were of the hilar group. The circumscribed group made up the other one-fourth and were of the parenchymal type.

SYMPTOMATOLOGY:

It might be well to consider in the beginning that the symptomology of bronchogenic carcinoma may be masked by extra pulmonary symptoms due to distant metastases. This is of grave importance because in Arkin and Wagner's series of 135 cases reported in 1936 only 49 per cent showed pulmonary symptoms early while the remaining 51 per cent were extra-pulmonary. They classified this extra pulmonary group as to structures involved and frequency of metastases. The osseus group comprised 16 per cent; cerebral, 10 percent; cardiac, nine per

cent; gastrointestinal, eight per cent; lymphoglandular, six per cent; and, hepatic, two per cent. However, in this discussion, symptoms will be limited mainly to the pulmonary type. Symptoms will be given in the order of their frequency.

The onset is almost always insiduous. However, the onset may be abrupt, being ushered in by an acute inflammatory condition; this being bronchitis, pneumonia or pleurisy. Polveski, in 1929, made the statement that in regard to bronchogenic carcinoma one should always become suspicious of recurring attacks of pneumonia or of the history that a patient has not been well since a previous attack of pneumonia when it is evident that all residual signs should have disappeared.

Cough is undoubtedly the first symptom as shown by Simons in 1937. He analyzed 1,376 cases in which it was present in 72.3 per cent of the cases. This cough usually is dry at first and as it progresses becomes productive and as the tumor ulcerates, frequently becomes blood-stained. Blumgarten, in 1921, tried to show the relation of the type of cough to the location of the neoplasm. He stated that the cough was dry in the pleural type and productive in the hilar. This may be true early but late in the course of the disease almost all become productive.

Expectoration is the second commonest symptom. Simons (1937) in his compilation of 1,217 cases found it present in 67.5 per cent of the total cases. This expectoration at first is usually thin, while later it becomes more tenacious, purulent and even blood-streaked.

Pain is a very common symptom and in Simons (1937) analysis of symptoms found that it comprised 59.8 per cent of 1,439 cases. This pain is persistent and relief is gained only by the use of opiates and not by some of the other methods commonly used. Polveski, in 1929, stated that he believed pain was the commonest symptom elicited and was the one which usually directed the patient to his condition. He further pointed out that pain was exceptional in secondary carcinoma of the lung. Bonner, in 1930 remarked that persistent and severe chest pain in the absence of a pleurisy is pathognomonic by primary lung tumor.

Dyspnoea, in Simons (1937) analysis of 1,299 cases, was present in 59.7 per cent of them. Polveski, in 1929, felt that next to pain, dyspnoea was the commonest symptom, which brought the patient's attention to his condition. As can be realized, this dyspnoea may arise from numerous factors. It may be due to actual compression of lungs, heart, or vessels. Again it may be

due to complicating atelectasis or pleural effusion.

According to Simons (1937) the symptom of emaciation was present in 48.2 per cent of 1,187 cases. This may occur early or late. Pyrexia occurred in 42.8 per cent of 1,112 cases analyzed by Simons.

Hemoptysis occurred in only 40 per cent of 1,456 cases analyzed by Simons. This may vary from blood-streaked sputum to frank hemorrhage. According to Brockbank, in 1931, the persistent absence of tubercle bacilli in a middle-aged patient with hemoptysis is one of the most useful signs in diagnosis.

Other symptoms in their order of frequency as analyzed by Simons are: dilated veins, cyanosis, edema, night sweats, clinical secondary deposits, vomiting, dysphagia, hoarse, and, lastly, clubbed fingers.

PHYSICAL FINDINGS:

As can readily be seen, these can be and are very varied, and, Andrus, in 1935, remarked, they are almost always due to secondary changes. Several men have described what they call physical signs pathognomonic of bronchiogenic carcinoma, Neumann, in 1924, gave the following physical findings as those that are pathognomonic. With carcinoma in the upper lobe, percussion reveals with normal apex area, almost complete dulness

in the median half of the infraclavicular fossa. Auscultation shows no bronchial breathing, amphoric sounds or rales, diminished or absent vesicular breathing.

Golden, in 1925, remarked that bronchogenic carcinoma develops in two stages as far as physical effects are concerned. First, there is the stage of invasion and, secondly, the stage of bronchostenosis, characterized by bronchiectasis, infection, atelectasis and pleural thickening, with or without fluid.

Blumgarten, in 1921, considered the physical signs very simply and stated that the peripheral type are largely pleural and often with a one-sided effusion. He said that the hilar-type gives signs of compression. This is stated simply but an analysis of the facts shows that it covers a "multitude of sins" and that is exactly the way the physical finding of bronchogenic carcinoma should be considered.

Brockbank, in 1931, considered the presence of ronchi localized to one side of the chest pathognomonic. However, the present day clinicians consider that the best evidence in physical diagnosis of bronchogenic carcinoma is not to be found in any one set group of physical findings but in an ever-changing picture from day to day, such as, finding atelectasis at one examination and bronchiectasis at the next.

ROENTGENOLOGICAL ASPECTS:

It was with the advent of improved technique and wider use of the x-ray that improvement in the diagnosis of bronchogenic carcinoma has, in a large part, been made. It, however, must be realized that seldom are the x-ray findings, alone, enough to make a positive diagnosis but, as Childs, in 1923, pointed out, should be combined with clinical and laboratory evidence.

From the fluoroscopic standpoint, x-ray has been extremely valuable in differentiating solid tumor from aneurysm due to the motion of the latter. Polveski, in 1929, considered a picture, such as the following, as pathognomonic of pulmonary cancer: high position of the diaphragm on the affected side; paradoxical repirations with a "seesaw" movement of the diaphragm, and pendulum movement of the heart toward the side of the lesion in inspiration and away from it in expiration.

Roentgenological characteristics were well outlined by Kirklin and Paterson in 1928. They state that these characteristics are two-fold, that is, density at the hilum with an atelectatic and/or bronchiectatic appearance. They stated that the density at the hilum is of more importance. As the lesion grows, they devised the following classification to fit the secondary picture: (1) stenotic, (2) infective, (3) pleuritic, or

(4) metastatic. They stated that the diagnosis cannot be made from the x-ray alone but also the clinical history must be considered and bronchoscopy done. Mediastinal Hodgkin's disease or lymphosarcoma may confuse the picture but they point out that the latter two present rounded edges at their periphery while bronchogenic carcinoma gives a picture of infiltration.

Burrell, in 1930, reported a case in which a small carcinoma, pedicled, was removed by incision. This was of interest because of the confusing picture of atelectasis produced in the x-ray when actually the tumor was small and operable. This picture of atelectasis is so important that Farrell, in 1936, propounded the axiom that when atelectasis is present, it should be considered as due to intrabronchial neoplasm until proven otherwise.

Manges, in 1930, mentioned, in relation to mediastinal shift, that the presence of a mass, rounded or infiltrative, with a shift of the mediastinal structures to the affected side is the chief roentgenologic sign.

Of course, in differential diagnosis, one must consider many things and it should be understood that the diagnosis should never be made positively with an x-ray film or fluoroscopic study. With the advent of modern methods of direct study of the bronchi, that is the bronchoscope, there must be, as Berger, in 1934,

remarked, complete cooperation between the clinician, roentgenologist and bronchoscopist to diagnose, correctly, bronchogenic neoplasms.

BRONCHOSCOPIC ASPECTS:

The advent of the bronchoscope, in conjunction with the x-ray, has done more in aiding in raising the percentage of antemortem diagnoses than any other one thing. This easily is understood, when one considers that with this instrument, the exact tissue is brought into view and a section of that tissue is available. As Jackson, in 1930, said, bronchoscopy is the only means by which the diagnosis of an endobronchial new-growth can be made. It can be made early and with all the certainty of modern histologic methods. One author, in speaking of the hesistancy in the use of the bronchoscope, said that the urologist never hesitates to use the cystoscope in any genito-urinary complaint and feels that the bronchoscopist should have the same attitude toward any pulmonary complaint.

To evaluate the accuracy of the bronchoscope, Kramer and Som, in 1936, reported 300 cases of pulmonary carcinoma on which bronchoscopic examinations were made and showed that 222 cases or 74 per cent were diagnosed by biopsy. This substantiates Jackson, who stated that a

bronchoscopic exam will be positive in 75 per cent of cases.

Jackson and Konzelmann, in 1937, remarked that the chief indication for bronchoscopy, is either the clinical or roentgenologic evidence of bronchial obstruction. This is further of benefit because the experienced bronchoscopist can locate the lesion for the surgeon or radiologist, thus directing their approach to therapy.

Although Vinson and Moersch, in 1928, stated that bronchoscopy is the safest method of making a diagnosis of early bronchogenic carcinoma, it is not without its dangers. Green, in 1924, brought up a hitherto unregarded problem. Following bronchoscopy, his case had a marked febrile reaction, presumably due to the stirring up of a latent inflammatory process in the lung. Wood, Spake, Summerville and Tice, in 1935, listed what they considered contraindications of bronchoscopy in suspected bronchogenic carcinoma: (1) contraindicated until a careful history had been taken, complete physical examination done and all laboratory work done; (2) contra-indicated in the presence of an aneurysm; (3) contra-indicated after severe hemorrhage; (4) contra-indicated if the patient is moribund.

It must be realized that bronchoscopy is not infalliable. Rabin and Neuhof, in 1934, pointed out that it

might be necessary to make repeated examinations and biopsy to prove either the presence or absence of carinoma. Vinson, in 1929, while discussing the differentiation between primary carcinoma of the lung and unusual types of pulmonary tuberculosis, showed that at bronchoscopy and biopsy there might be a resemblance to carcinoma and yet positive or presumptive evidence might give aid in the establishment of a diagnosis of tuberculosis of the lung. In further discussing errors at biopsy, Eggers, in 1934, reported the case of a boy, twelve years of age, on whom a biopsy, via the bronchoscope, was done. This was diagnosed, pathologically as carcinoma. The growth was destroyed by use of the diathermy and the boy, two years later, has shown no recurrence or metastases. Eggers remarked that these tumors may be carcinoids similar to that seen in the appendix and urged that all such cases submit slides to the Chest Tumor Registry for study. This raises a very important question as to the possibility of treating such tumors by the bronchoscope and certainly enhances the prognosis when proven at biopsy. A more careful search may reveal the presence of such a tumor and this is important because of its benignity. It can readily be seen that with the use of the bronchscope, it is not always possible to visualize the superior bronchi due to the technical pro-

cedures involved in turning corners at such an acute angle. This is trying to be remedied at the present time by inserting a set of mirrors into the scope so as to produce vision at angles to the position of the instrument.

In conclusion, it is well to again emphasize the importance of the bronchoscope in bronchogenic carcinoma, not only from the standpoint of diagnosis, but also as a guide in treatment and use in prognosis. The axiom of Hodge (1930) might well be remembered, that is, that a patient deserves a bronchoscopic examination in any "bizaree pulmonary conditon."

OTHER LABORATORY PROCEDURES:

Brockbank, in 1931, remarked about the onset of pleural effusion in an elderly patient, and believed that it was particularly significant if that fluid was bloody. Goltz, in 1930, believed that one-half of all patients with primary pulmonary carcinoma show a pleural effusion and he believed that one third of these are hemorrhagic. Jaffe', in 1935, found, after reviewing 100 cases that had come to autopsy, that 43 of these cases showed pleural effusion. Of these 14 were serous, 13 were hemorrhagic, 12 suppurative and four were fibrinous. Blumgarten, in 1921, believed that in case of a pleural effusion, there should be an examination of that

fluid made. He recommended centrifuging of the fluid and taking the sediment and imbedding it in paraffin. Following this, examination of serial sections should be done searching for malignant cells. With the frequency of cough in pulmonary carcinoma cases one could expect to find at times malignant cells in the sputum. Dudgeon and Wright, in 1935, worked on this problem and could in twenty out of twenty-six cases of definite bronchogenic carcinoma demonstrate the histologic type of neoplasm by the wet film method of examination of the sputum.

Blood studies offer little in the diagnosis of this neoplasm. Sometime during the disease one may expect secondary anemia that is common to all malignancies, after a period. As has been mentioned before, Arkin, in 1930, believed that a myeloid blood picture should be sought for in every case.

DIAGNOSIS:

In considering diagnosis, one is immediately confronted with the fact that few cases of bronchogenic carcinomas are diagnosed during life or diagnosed early enough so that therapy is of any avail. There is evidently a solution to this problem and this is no doubt in a way related to the inadequate education of the medical profession on this subject. It is only in the medical centers which are "lung tumor conscious" that a fairly high

percentage of antemortem diagnoses are made. Eloesser, in 1925, reported 21 cases, ten of which were correctly diagnosed before death. Woods, Spake, Summerville and Tice, in 1935, presented 16 cases. Of these, nine were correctly diagnosed before death, two were suspected and five missed. Jaffe', in 1935, in his study of 100 autopsies of bronchogenic carcinoma showed that 59 were diagnosed correctly before death. Andrus, in 1935, showed by his review of his 64 cases, the diagnoses made during life, of what was shown to be definitely primary carcinoma of the lung at autopsy, nine were called pleurisy, nine bronchiectasis or lung abscess in seven, bronchitis in four, pleural effusion in three, and atelectasis, influenza, lung fibrosis, asthma, echinococic cyst, arthritis and gallbladder disease in one each.

Simons, (1937) quoted Bergmark as to his comments on the reasons for so many mistaken diagnoses. First, carcinoma of the lung is misleading because it simulates tumors of a different nature in the thoracic region, such as mediastinal swellings, cancer of the esophagus and aortic aneurysm. Second, it irritates lung inflammatory diseases, more markedly when secondary changes have occurred. Third, primary carcinoma of the lung, more frequently than any other carcinom, give a picture

of cardiac insufficiency. Fourth, due to widespread metastases, symptoms of nervous septem, bone or liver metastases mark the true picture. Fifth, that in this tumor, general symptoms predominate the picture. Due to the confusing picture, Thacker, Neville, in 1929, urged for better diagnosis, that in any patient with a persisten and chronic cough showing a degree of hemoptysis with a negative sputum should be subjected to a thorough bronchoscopic examination.

All the symptomatology and technical procedures available have been briefly reviewed previously. However, it might be well at this point to correlate these into a less confusing picture. If one keeps constantly in mind the value of the bronchoscope in this condition and that approximately 75 per cent of all cases can be definitely diagnosed this way, one has gone a long way in increasing the percentage of antemortem diagnoses and likewise prognosis. However, in conjunction with the bronchoscope, roentgenology must be kept in mind a and used to further aid in the diagnosis of the disease. Too much emphasis must not be put on these two procedures without first considering the careful history and physical examination. This should lead the careful physician to a further search for the seat of the trouble.

This further search should consist of x-rays, repeated sputum examinations, study of the pleural effusions, if present, study of the blood picture and finally the bronchoscopic examination with the biopsy. If this routine would be followed more meticulously, there would be a definite increase in the diagnoses with a consequent decrease in mortality due to the institution of the known therapy.

Differentiated Diagnosis:

The most difficult disease to differentiate bronchogenic carcinoma from is tuberculosis. Simons (1937), compiled a table, attempting to differentiate the two diseases.

CARCINOMA	TUBERCULOSIS
Often no fever	Fever usually present
Tachycardia rare until late	Tachycardia usually present
Dyspnoea common	Dyspnoea rare until late
Pain common	Little pain except with pleurisy
No history of previous attacks	History of previous attacks, after 40 is selfom first attack.
Usually spares apices	Most often involves apices
Unilateral	Often in late stages bilateral
Impaired resonance with absent or diminished breath sounds	Impaired resonance often accompanied by bronchial breathing.
Impaired resonance is usually "flatness". Rales seldom heard. Bulging of chest infrequent	Impaired resonance is usually "dulness". Rales usually heard. Flattening of chest frequent.

Further diagnostic procedures are used to differentiate these two diseases. Repeated examinations of the sputum, if done carefully, usually reveal the presence or absence of tuberculosis.

For further differential diagnosis, bronchiectasis, abscess and gangrene of the lung, pleurisy with effusions, unresolved pneumonia, gumma of the lung, echinococcic cysts, carcinoma of the trachea and esophagus, Hodgkin's disease, lymphosarcoma and the various leukemias must be considered. These may be all ruled in or ruled out by careful roentgenological studies, bronchoscopy, aspiration and microscopic studies of material removed, gland biopsy, lipiodol insufflation and pneumothorax. Of course, a careful serologic study must be made in every case.

PROGNOSIS AND COURSE:

Regardless of the advances made in thoracic surgery and irradiation therapy, the prognosis of this disease must still be considered as very poor. However, to fully evaluate the prognosis, the histologic type of cell must be know and as Tuttle and Womack, in 1934, pointed out, the topographic location is of importance. They said that tumors arising from the major bronchi give earlier symptoms but spread more

slowly while those of the periphery and minor bronchi give late symptoms with an early spread.

Jaffe', in 1935, maintained that the hilar type of tumor has a life duration, on the average, of eight months while those having the peripheral type live five months.

However, life may be ended early, not from the tumor itself, but due to a pneumonia peripheral to the growth of the tumor. Death may occur and quite frequently does, from the metastatic involvement of some other organ. If the patient escapes the above, he will go on the the cachexia and debilitation common to all malignancies.

TREATMENT

In considering the treatment of bronchogenic carcinoma, it is readily seen that is consists of the same line of therapy as any malignant disease, that is, extirpation of the diseased organ and irradiation. However, if metastases have occurred, there only remains the choice of palliative measures to make the patient more comfortable and possibly the use of irradiation on the metastatic growths.

Overholt, in 1937, said that Gluck, in 1881, performed the first pneumonectomy on animals. Thirty years later, Kummell attempted a pneumonectomy on man but the operation was unsuccessful., Hinz, in 1923, reported the removal of an entire lung on a man, age 56, who had pulmonary carcinoma. This man, however, died on the third post-operative day of pulmonary emphysema. Hinz at this time showed that there were nine partial pneumonectomies on record with five who lived.

Overholt, in 1937b, stated that extirpation of any cancer bearing organ before metastases had occurred gave the best chance of cure. In discussing the problem of surgery on the lung, he places the credit of the improval in thoracic surgery on the recent advances in anaesthesia, a better understanding of the

physiology of the lung, better operative technique and better post-operative care. He cited the mort-tality at being 15 per cent for lobectomy and 35 per cent for pneumonectomy. He stated that for the past ten years, lobectomy has been in mode while pneumon-ectomy has been used for five years.

It can readily be seen that lobectomy runs less mortality than pneumonectomy. The concensus of op-inion, at the present time, however, is that pneumon-ectomy is the procedure of choice. This is explained by Overholt, in 1937z, by showing that the relative frequency of the site of the tumor's origin in a main stem bronchus is such that dissemination occurs through-out the lung rather than being confined to one lobe. Therefore, to offer the most to the patient the whole lung should be removed so as to avoid any unforeseen recurrences in an unsuspected lobe.

Surgical exploration of the thorax has become so efficient with a definite lowering of mortality, that Overholt, in 1938, stated that the peripheral growth of the lung could simulate so many other pathological processes and he believes that surgical exploration is definitely indicated when this is seen.

To evaluate the success of these operations, a

few cases will be cited. Allen, in 1935, reported a case on which a right lower lobectomy had been performed four years previously. The patient was in good health except for a paroxysmal cough. During these four years, the patient had had periodic bronchoscopic examinations with implantation of radium into a new growth in the stump of the right bronchus. Andrus, in 1935, reported 26 cases on which operative procedures had been done. Exploratory thoracotomy was used in 13 cases, six cases of cautery pneumonectomy and four cases in which the entire lung was removed. Of the four cases of total pneumonectomy, one patient died at seven weeks, one was well after six weeks, one was well after seven months, and one was well after two years. Rabin and Newhof, in 1934, reported five cases of lobectomy in which the longest period of survival was one year.

BRONCHOSCOPY:

The bronchoscope has come into play as a therapeutic agent as well as a diagnostic one. There have been numerous reports in the literature of the removal of a small neoplasm from the bronchus via this instrument. This, however, must receive more consideration because it would seem that rarely would one expect a cure if the

neoplasm excised was carcinomatous in nature.

Orton, in 1924, reported the removal of a carcinoma from the bronchus via the bronchoscope and a complete relief of symptoms after a short interval. Burrell, in 1929, reported the removal of a pedicle adencarcinoma through a bronchoscope with the immediate relief of symptoms of atelectosis. He raised the question then as to whether whole tumor was removed or not.

Not only for the removal of the neoplasms is the bronchoscope used. It is also a definite value for the implantation of radium. Besides the case reported above by Allen, in the implantation of radium into the bronchial stump of a previously removed lobe, Kernin, and Cracovaner, in 1929, reported a case in which a tumor was seemingly entirely removed by the use of radium seeds and the application of the surgical diathermy through the bronchoscope.

In the final analysis, the bronchoscope cannot be considered of too great a value in the therapy in this condition because of the few tumors of this type which can be treated in this method. Pneumonectomyy and lobectomy offer much more for a favorable prognosis.

IRRADIATION THERAPY:

Considering this phase of treatment, there are many things to consider. The main problem is whether irradiation is an actual cure or whether it is only palliative in its effects. There is no doubt but what the combination of surgery and irradiation offers the most. Mattick, in 1938, stated that neither radical surger nor irradiation therapy seems at present to warrant much optimism. He stated further that due to the early and widespread metastases, better planned radiation therapy offers the best hope.

Vinson, in 1936, reported 71 cases of which eight survived four years following intensive therapy by irradiation and six of these were living from four to seven and one-half years after treatment. In another group of 69 patients, four are living and in good condition, one at ten months, two at elemen months and one at thirty months. In the group of 71 patients, 30 patients who were not treated lived on the average of six months. Vinson concluded that although the treatment was not startling or brilliant, the fact that ten of the above patients were very much improved or cured after irradiation, warrants the use of this therapy whenever possible.

In regard to irradiation of metastatic lesions, it may be seen that this offers little in the way of

cure but certainly would be of aid in the alleviation of pain when such lesions exist. Winslow, in 1931, reported a case which had stood from June, 1926, to November, 1930. He stated here that the average life duration is from six months to two years. This life was prolonged and metastases prevented by deep roentgen-ray therapy.

In concluding this subject of treatment, the work of Ochsner and DeBakey, in 1939, is worthy of note. These authors reviewed the total of 79 reported cases for malignancy of the lung, all treated by total pneumonectomy. They add to this seven cases of their own making a total of 86 cases. Of these 86 cases, 55 died and 31 recovered. Of these 31 recoveries, five died later of metastases. In summarizing this work, it is found that the mortality for total pneumonectomy in cases of primary malignancy of the lung, at the present time, is 64 per cent. Further, it must be realized that of the 36 per cent who survive the surgery, 16 per cent will die later of metastases.

SUMMARY AND CONCLUSIONS

In final consideration of primary pulmonary carcinoma, the following conclusions have been reached.

(1) Facts and figures have been cited that prove definitely that primary carcinoma of the lung has shown a real increase in incidence, rather than apparent.

(2) Fourteen etiologic agents have been discussed, any one of which produce chronic pulmonary irritation. The final summation is that the only etiologic factor is chronic irritation regardless of whether it is mechanical, chemical, bacterial or radioactive.

(3) It has been shown that all primary pulmonary carcinomas are to be considered bronchogenic.

(4) A large number of figures have been shown so as to conclude that the sex incidence is four males to one female.

(5) The age incidence has been found to be 80.4 per cent of cases occur between the ages of 40 and 70.

(6) The commonest symptoms in the order of their frequency are: cough, expectoration, pain, dyspnoea, emaciation, fever, and hemoptysis.

(7) Physical findings are not pathognomonic but give a picture of secondary changes.

(8) The two most important adjuncts to diagnosis are the x-ray and bronchoscope when used in conjunction with each other.

(9) Treatment has been considered from three angles, roentgenologically, bronchoscopically and surgically. Surgery offers the most to effect a complete cure.

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